

REMARKS/ARGUMENTS

Claims 1-16 are active. Claims 1-3 have been amended as method of treatment claims to conform to U.S. practice. The Examiner has examined the case based on an interpretation of claims 1-3 as method of treatment claims (see OA, top of page 3). New dependent claims 4-7 are directed to specific substituents already described by claim 1 and find support in the original claims. New claims 8-16 are directed to treatment of human pathologies and specific diseases and disorders disclosed at the top of page 6 of the specification. Accordingly, the Applicants do not believe that any new matter has been introduced.

The Applicants thank Examiner Ramachandran for the courteous and helpful interview of March 24, 2009. Ways to address the prior art rejections by directing the claims to treatment of particular subgroups of subjects, i.e., those subjects having neuropathic pain as opposed to nociceptive pain, or subjects having specific diseases or disorders characterized by significant neuropathic pain, were discussed. The Examiner advised showing a clear nexus between neuropathic pain and any particular disease named in a dependent claim, for example, by submission of a scientific review article.

Diseases and Disorders Characterized by Neuropathic Pain

| claim | Disease causing neuropathic pain | Scientific Review or Reference   |
|-------|----------------------------------|--|
| 9     | diabetes                         | Ahmad, et al., Drugs Aging 19(12):929-945; see abstract and paragraph 3.3.4.<br>Galluzzi, JAOA 107(11):ES39-48, see ES39, first paragraph and Table 1<br>Sadosky, et al., Pain Prac. 8(1):45-56, see page 46, cols. 1-2.<br>Veves, et al., Pain Med. 9(6): 660-674, see entire.<br>Tremont-Lukats, et al., Drugs 60(5):1029-52, Intro, pages 1030-31.<br>Paice, Supp. Oncol.. 1(2):107-120, page 109, table 1. |
| 10    | immunodeficiency                 | Galluzzi, <i>id.</i> Sadosky, et al., <i>id.</i> see page 47, cols. 1-2.   |

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|----|------------------------|--|
|    |                        | <u>Verma, et al.</u> , CNS Drugs 19(4):325-334, see entire.<br><u>Gray</u> , Curr. Opin. Anaestol. 21:590-595, page 590, col. 2. <u>Paice, id.</u>                     |
| 11 | trauma                 | <u>Galluzzi, id.</u> , <u>Sadosky, et al.</u> , <i>id.</i> , page 47, col. 1.; <u>Gray, id.</u> , page 591, col. 1.; <u>Finnerup</u> , Curr. Opin. Anaesth. 21:586-89. |
| 12 | ischaemia              | <u>Galluzzi, id.</u>   |
| 13 | multiple sclerosis     | <u>Galluzzi, id.</u> ; <u>Sadosky, et al.</u> , <i>id.</i> , page 51, col. 2 "spinal cord injury". <u>Finnerup, id.</u>  |
| 14 | sciatic neuralgia      | <u>Ahmad, id.</u> ; <u>Tremont-Lukats, et al.</u> , <i>id.</i>   |
| 15 | trigeminal neuralgia   | <u>Galluzzi, id.</u> ; <u>Sadosky, et al.</u> , <i>id.</i> , page 47, bottom of col. 2. <u>Paice, id.</u>  |
| 16 | post-herpetic syndrome | <u>Ahmad, id.</u> ; <u>Galluzzi, id.</u> , <u>Sadosky, et al.</u> , <i>id.</i> , page 47, col. 1.; <u>Tremont-Lukats, et al.</u> , <i>id.</i> ; <u>Paice, id.</u>      |

Priority & Information Disclosure Statements

The Applicants thank Examiner Ramachandran for acknowledging the priority claim and the previously-filed information disclosure statements.

Rejection—35 U.S.C. §101

Claims 1-3 were rejected under 35 U.S.C. 101, as being directed to non-statutory subject matter. This rejection is moot in view of the amendments above.

Rejection—35 U.S.C. §112, second paragraph

Claims 1-3 were rejected under 35 U.S.C. 112, second paragraph as indefinite. This rejection is moot in view of the amendments above. The Applicants thank the Examiner for construing the claims as method of treatment claims and initiating examination.

Differences between Nociceptive Pain, Neuropathic Pain and Psychogenic Pain

The art recognizes at least three different types of pain caused by different mechanisms: contact with pain-causing physical or chemical agents (nociceptive pain), damage to the nervous system itself (neuropathic pain), or pain caused or associated with

emotional, behavioral, or mental factors (psychogenic pain). Neuropathic pain is a distinct type of pain as shown by references AQ, AR, AT and AU on the information disclosure statement dated January 17, 2006 and by the references cited in the Table above, attached to this response. The distinction between nociceptive pain, neuropathic pain and psychogenic pain is summarized by Wikipedia (<http://en.wikipedia.org/wiki/Pain>)(attached):

**Stimulation of a nociceptor**, due to a chemical, thermal, or mechanical event that has the potential to damage body tissue, may cause **nociceptive pain**.

**Damage to the nervous system itself**, due to disease or trauma, may cause **neuropathic (or neurogenic) pain**.<sup>[11]</sup> Neuropathic pain may refer to peripheral neuropathic pain, which is caused by damage to nerves, or to central neuropathic pain, which is caused by damage to the brain, brainstem, or spinal cord.

Nociceptive pain and neuropathic pain are the two main kinds of pain when the primary mechanism of production is considered. A third kind may be mentioned: see below **psychogenic pain**.

Nociceptive pain may be classified further in three types that have distinct organic origins and felt qualities.<sup>[12]</sup>

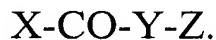
1. Superficial somatic pain (or cutaneous pain) is caused by injury to the skin or superficial tissues. Cutaneous nociceptors terminate just below the skin, and due to the high concentration of nerve endings, produce a sharp, well-defined, localized pain of short duration. Examples of injuries that produce cutaneous pain include minor wounds, and minor (first degree) burns.
2. Deep somatic pain originates from ligaments, tendons, bones, blood vessels, fasciae, and muscles. It is detected with somatic nociceptors. The scarcity of pain receptors in these areas produces a dull, aching, poorly-localized pain of longer duration than cutaneous pain; examples include sprains, broken bones, and myofascial pain.
3. Visceral pain originates from body's viscera, or organs. Visceral nociceptors are located within body organs and internal cavities. The even greater scarcity of nociceptors in these areas produces pain that is usually more aching or cramping and of a longer duration than somatic pain. Visceral pain may be well-localized, but often it is extremely difficult to localize, and several injuries to visceral tissue exhibit "referred" pain, where the sensation is localized to an area completely unrelated to the site of injury.

The method claimed in this application pertains to treatment of **neuropathic pain** caused by damage to the nervous system.

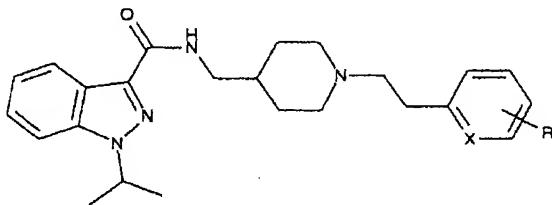
Rejection—35 U.S.C. §103(a)

Claims 1-3 were rejected under 35 U.S.C. §103(a) as being unpatentable over King, et al., WO93/03725, in view of Uchida, et al., U.S. Patent No. 6,624,162. These references cannot render the claimed methods of treating neuropathic pain obvious because they do not suggest or provide a reasonable expectation of success for treating subjects exhibiting neuropathic pain with the compounds of formula (I) required by the claims.

King is cited as disclosing compounds of formula (I) on page 2. Page 2 of King discloses a large genus of compounds of the formula:



Formula (I) required by present claim 1 is:



(I)

The compound of formula (I) falls within the genus of King, when X is selected to be group (a) (as opposed to ring structures b or c), where L is selected to be N (and not CR<sub>s</sub>), Q is selected to be NR<sub>1</sub> (instead of CH<sub>2</sub>, O or S) and R<sub>1</sub> is selected to be isopropyl (as opposed to hydrogen or numerous other alkyl, alkenyl, alkanoyl or alkanoyl-alkyl groups)—see pages 2 and 3 of King.

While King generically embraces formula (I), it does not specifically describe compounds of formula (I), for example, by pointing out the specific substituents required to make formula (I). It is worth noting that none of the numerous compounds exemplified by King correspond to formula (I) in pending claim 1. For example, only the compounds of

Examples E1, E6, E10-E14, E16-E18, E20, E22, E24, E26, E29, E32-E34, and E36-E41 contain ring (a). However, only the compound of E10 contains N at positions L and Q as required by formula (I), but contains O (oxygen) at position Y instead of the N in formula (I) and contains and its Z group does not correspond to that of formula (I). Moreover, position Q in ring (a) in E10 is not substituted with isopropyl. The other compounds exemplified on page 49 of King do not contain N at position L and thus do not conform to formula (I) of the invention. Pages 50-51 of King which describe three 5-HT<sub>4</sub> receptor antagonist activity assays, do not disclose whether or not the closest exemplified compound to formula (I)—that of E10—exhibits any 5-HT<sub>4</sub> antagonism.

The Examiner indicates that King does not disclose or suggest using a compound of X-CO-Y-Z to treat **neuropathic pain**, however, King is applied as disclosing that this class of compounds exhibits antagonism for 5-HT<sub>4</sub> receptors which potentially might be used to treat IBS, atrial arrhythmias and stroke (see King, top of page 2).

Uchida does not disclose the compounds of formula (I) of the invention, but has been applied as a secondary reference disclosing that 5-HT<sub>4</sub> modulators (agonists or antagonists) for treatment of the diseases described in claims 10 and 11 in col. 56 (see also col. 25, lines 9-21). However, neither Uchida and King disclose or suggest using compounds of formula (I) to treat neuropathic pain, nor even that 5-HT<sub>4</sub> antagonists reduce neuropathic pain. Therefore, these references could not have provided a reasonable expectation of success for treating a subject exhibiting neuropathic pain using a 5-HT<sub>4</sub> antagonist, or *a fortiori* (for an even stronger reason) selecting a compound of formula (I) for this purpose.

The rejection assumes that:

- (i) the compound of formula (I) is a 5-HT<sub>4</sub> antagonist,
- (ii) 5-HT<sub>4</sub> agonists have activity on the diseases disclosed by Uchida, and
- (iii) neuropathic pain is an essential characteristic of the diseases named by Uchida.

The Examiner has applied no art that discloses that the compound of formula (I) is a 5-HT<sub>4</sub> antagonist. King only indicates that “certain of these compounds. . .act as 5-HT<sub>4</sub> antagonists (emphasis added)”. Page 6, lines 19 *ff.* of King indicate that “5-HT<sub>4</sub> receptor antagonist activity may be identified according to standard methods”. Moreover, pages 50 and 51 of King provide specific assays useful for identifying which compounds falling within the genus of compounds X-CO-Y-Z actually have 5-HT<sub>4</sub> receptor antagonistic activity. Based on these teachings of King, one of skill in the art at the time of invention would have deduced that not all compounds falling within the genus X-CO-Y-Z exhibit 5-HT<sub>4</sub> antagonism. Not only does King not suggest that compounds of formula (I) are 5-HT<sub>4</sub> antagonists, it provides no suggestion or reasonable expectation of success that these compounds would treat neuropathic pain. Assuming *arguendo* that King demonstrated that compounds of formula (I) were 5-HT<sub>4</sub> antagonists, it did not suggest or provide a reasonable expectation of success for treating neuropathic pain using these compounds. Uchida, which provides a list of diseases that might be treated with 5-HT<sub>4</sub> antagonists, also does not show that compounds of formula (I) would treat neuropathic pain, or even that the listed diseases are characterized by neuropathic pain.

On the other hand, the Applicants have shown that compounds of formula (I) actually reduce neuropathic pain (pain caused by damage to the nervous system) using at least two different animal models of neuropathic pain. Both Examples 1 and 2 of the present application specifically employed two different models for neuropathic pain and demonstrated that the compounds of the present invention were actually able to reduce the neuropathic pain induced by such models (see pages 5-6 for a discussion of such models and pages 6-8 together with Figures 1 and 2 for the results).

Specifically, the models employed in the present application were (i) allodynia induced by ligature of the sciatic nerve and (ii) mechanical hyperalgesia in diabetic

neuropathy induced by streptozotocin. Both models were widely known in the art to be predictive of neuropathic pain in humans.

In contrast, Uchida did not provide any data from an animal model or clinical results of treating any of the diseases it describes. The biological activities demonstrated by Uchida were limited to the ability of their compounds (which differ from formula I of the present invention) to bind 5-HT<sub>4</sub> receptor, without any demonstration of therapeutic activity (see col. 25, line 25 through col. 28, line 27). Whether or not these compounds would have any effect on disease by virtue of their 5-HT<sub>4</sub> antagonism was speculation. Therefore, Uchida would not have provided a reasonable expectation of success for the present invention because it did not disclose compounds of formula (I), did not indicate that compounds of formula (I) are 5-HT<sub>4</sub> antagonists, did not indicate that 5-HT<sub>4</sub> antagonists--or specifically the compounds of formula (I)--have any useful activity *in vivo* or that they treat the group of diseases disclosed by Uchida, or disclose or provide any reason for believing that compounds of formula (I) would treat neuropathic pain.

Moreover, the written opinion for the corresponding PCT application--PCT/EP2004/007635—clearly acknowledges that neuropathic pain and inflammatory pain involve different mechanisms and require different treatments by reference to Donahue et al., Brain Res., 897: 131, “Electrolytic lesion of the anterior cingulated cortex decreases inflammatory, but not neuropathic nociceptive behavior in rats”. As apparent from the title of this document, those of skill in the art distinguished between nociceptive pain (e.g., inflammatory pain, formalin text, page 132, col. 1, lines 14 *ff.*) and neuropathic pain caused by nerve injury (tight ligation of the L5 spinal nerve, page 132, col. 1, lines 5 *ff.*). These results show that nociceptive (here inflammatory) pain and neuropathic pain are mediated by different mechanisms. Based on these results, those of skill in the art would understand that

different biological models would be required to establish the efficacy of drugs for treatment of neuropathic pain as opposed to nociceptive pain.

Therefore, since the prior art does not disclose all the elements of the invention, namely treatment of subjects having neuropathic pain, does not establish that compounds of formula (I) are 5-HT<sub>4</sub> antagonists and does not establish that 5-HT<sub>4</sub> antagonists reduce neuropathic pain, this rejection cannot be sustained.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,  
MAIER & NEUSTADT, P.C.  
Norman F. Oblon



Thomas M. Cunningham, Ph.D.  
Registration No. 45,394

Customer Number  
**22850**

Tel: (703) 413-3000  
Fax: (703) 413 -2220  
(OSMMN 08/07)